

Applicant: LEAKE *ET AL.*
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Amendments to the Claims:

This listing will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. - 113. (canceled)

114. (currently amended) An siRNA, comprising:

(a) an antisense strand, wherein said antisense strand ~~is comprised of~~ comprises a first 5' terminal antisense nucleotide and said first 5' terminal antisense nucleotide is phosphorylated at said first 5' terminal antisense nucleotide's 5' carbon position; and

(b) a sense strand, wherein said sense strand ~~is comprised of~~ comprises a first 5' terminal sense nucleotide and a second 5' terminal sense nucleotide, wherein said first 5' terminal sense nucleotide comprises a first 2' carbon sense modification and said second 5' terminal sense nucleotide comprises a second 2' carbon sense modification.

115. (original) The siRNA of claim 114, wherein each of said first 2' carbon sense modification and said second 2' carbon sense modification is a 2'-O-alkyl modification.

116. (canceled)

117. (original) The siRNA of claim 115, wherein at least one of the 2'-O-alkyl modifications is a 2'-O-methyl modification.

118. (original) The siRNA of claim 115, wherein each of the 2'-O-alkyl modifications is a 2'-O-methyl modification.

119. (currently amended) The siRNA of claim 115, wherein said siRNA ~~is comprised of~~ comprises between 18 and 30 base pairs.

120. (currently amended) The siRNA of claim 119, wherein said siRNA is comprised of comprises between 19 and 25 base pairs.

121. (original) The siRNA of claim 119, wherein said antisense strand and said sense strand are substantially complementary and form a duplex that does not contain overhangs.

122. (currently amended) A method of reducing off-target effects during RNAi, said method comprising exposing an siRNA to a target nucleic acid, wherein said siRNA comprises an antisense strand and a sense strand, wherein:

- (a) said sense strand is comprised of comprises a first 5' terminal sense nucleotide and a second 5' terminal sense nucleotide, and wherein said first 5' terminal sense nucleotide comprises a first 2' carbon modification and said second 5' terminal sense nucleotide comprises a second 2' carbon modification; and
- (b) said antisense strand is comprised of comprises a first 5' terminal antisense nucleotide and said first 5' terminal antisense nucleotide is phosphorylated at said first 5' terminal antisense nucleotide's 5' carbon position.

123. (original) The method according to claim 122, wherein each of said first 2' carbon sense modification and said second 2' carbon sense modification is a 2'-O-alkyl modification.

124. (canceled)

125. (original) The method according to claim 123, wherein at least one of the 2'-O-alkyl modifications is a 2'-O-methyl modification.

126. (original) The method according to claim 123, wherein each of the 2'-O-alkyl modifications is a 2'-O-methyl modification.

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127. (currently amended) The method according to claim 122, wherein said siRNA is comprised of comprises between 18 and 30 base pairs.

128. (currently amended) The siRNA of claim 127, wherein said siRNA is comprised of comprises between 19 and 25 base pairs.

129. (original) The method according to claim 127, wherein said antisense strand and said sense strand are substantially complementary and form a duplex that does not contain overhangs.

130. (currently amended) A unimolecular siRNA capable of forming a hairpin, said unimolecular siRNA comprising:

(a) an antisense region, wherein said antisense region is comprised of comprises a first 5' terminal antisense nucleotide and said first 5' terminal antisense nucleotide is phosphorylated at said first 5' terminal antisense nucleotide's 5' carbon position;

(b) a sense region, wherein said sense region is comprised of comprises a first 5' terminal sense nucleotide and a second 5' terminal sense nucleotide, wherein said first 5' terminal sense nucleotide comprises a first 2' carbon sense modification and said second 5' terminal sense nucleotide comprises a second 2' carbon sense modification; and

(c) a loop region, wherein said loop region is located between said sense region and said antisense region.

131. (original) The siRNA of claim 130, wherein each of said first 2' carbon sense modification and said second 2' carbon sense modification is a 2'-O-alkyl modification.

132. (original) The siRNA of claim 130, further comprising a third 5' terminal sense nucleotide, wherein said third 5' terminal sense nucleotide comprises a 2'-O-alkyl modification.

133. (original) The siRNA of claim 131, wherein at least one of the 2'-O-alkyl modifications is a 2'-O-methyl modification.

134. (original) The siRNA of claim 131, wherein each of the 2'-O-alkyl modifications is a 2'-O-methyl modification.

135. (currently amended) The siRNA of claim 130, wherein said siRNA ~~is comprised of~~ comprises between 18 and 30 base pairs.

136. (currently amended) The siRNA of claim 135, wherein said siRNA ~~is comprised of~~ comprises between 19 and 25 base pairs.

137. (currently amended) A method for reducing off-target effects during RNAi, said method comprising: exposing a unimolecular siRNA that is capable of forming a hairpin to a target nucleic acid, wherein said unimolecular siRNA comprises an antisense region and a sense region, wherein:

(a) said sense region ~~is comprised of~~ comprises a first 5' terminal sense nucleotide and a second 5' terminal sense nucleotide, and wherein said first 5' terminal sense nucleotide comprises a first 2' carbon sense modification and said second 5' terminal sense nucleotide comprises a second 2' carbon sense modification;

(b) said antisense region ~~is comprised of~~ comprises a first 5' terminal antisense nucleotide and said first 5' terminal antisense nucleotide is phosphorylated at said first 5' terminal antisense nucleotide's 5' carbon position; and

(c) a loop region, wherein said loop region is located between said sense region and said antisense region.

138. (original) The method according to claim 137, wherein each of said first 2' carbon sense modification and said second 2' carbon sense modification is a 2'-O-alkyl modification.

139. (original) The method according to claim 138, further comprising a third 5' terminal sense nucleotide, wherein said third 5' terminal sense nucleotide comprises a 2'-O-alkyl modification.

140. (original) The method according to claim 138, wherein at least one of the 2'-O-alkyl modifications is a 2'-O-methyl modification.

141. (original) The method according to claim 138, wherein each of the 2'-O-alkyl modifications is a 2'-O-methyl modification.

142. (currently amended) The method according to claim 137, wherein said siRNA ~~is comprised of~~ comprises between 18 and 30 base pairs.

143. (original) The siRNA of claim 114 further comprising a second 5' terminal antisense nucleotide, wherein said first 5' terminal antisense nucleotide further comprises a first 2' carbon terminal antisense modification and said second 5' terminal antisense nucleotide comprises a second 2' carbon terminal antisense modification.

144. (original) The unimolecular siRNA of claim 130 further comprising a second 5' terminal antisense nucleotide, wherein said first 5' terminal antisense nucleotide further comprises a first 2' carbon terminal antisense modification and said second 5' terminal antisense nucleotide comprises a second 2' carbon terminal antisense modification.

145. (currently amended) A method of reducing off-target effects induced during RNAi, comprising introducing the siRNA of ~~any one of claims~~ claim 114 or 143 into a cell.

146. (currently amended) A method of reducing off-target effects induced during RNAi, comprising introducing the siRNA of claim [[144]] 143 into a cell.

147. – 151. (canceled)

152. (original) The siRNA of claim 150, further comprising a label.

153. (currently amended) A unimolecular siRNA capable of forming a hairpin, said unimolecular siRNA comprising:

- (a) an antisense region, wherein said antisense region ~~is comprised of~~ comprises a first 5' terminal antisense nucleotide and a second 5' terminal antisense nucleotide, wherein said first 5' terminal antisense nucleotide comprises a first 2' carbon antisense modification and said second 5' terminal antisense nucleotide comprises a second 2' carbon antisense modification;
- (b) a sense region, wherein said sense region ~~is comprised of~~ comprises a first 5' terminal sense nucleotide and a second 5' terminal sense nucleotide, wherein said first 5' terminal sense nucleotide comprises a first 2' carbon sense modification and said second 5' terminal sense nucleotide comprises a second 2' carbon sense modification; and
- (c) a loop region, wherein said loop region is located between said sense region and said antisense region.

154. (original) The siRNA of claim 153, wherein the sense region and the antisense region form a duplex of from 16–28 base pairs.

155. (original) The siRNA of claim 154, wherein the sense region and the antisense region form a duplex of from 18–25 base pairs.

156. (original) The siRNA of claim 154, wherein said first 2' carbon antisense modification, said second 2' carbon antisense modification, said first 2' carbon sense modification and said second 2' carbon sense modification each comprises a 2'-O-alkyl modification.

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157. (original) The siRNA of claim 156, wherein the 2'-O-alkyl modification is 2'-O-methyl.

158. (original) The siRNA of claim 156, further comprising a label.

159. - 200. (canceled)